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Original Article

Oral ulcer activity in Behcet's disease: Poor medication adherence is an underestimated risk factor

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Abstract

Objective: The aim of this study was to evaluate the relationship between oral ulcer activity and medication adherence according to gender in Behçet's disease (BD) patients.

Material and Methods: The study group included 330 BD patients (F/M: 167/163, mean age: 38.5±10.5 years). Oral ulcer activity and medication adherence were evaluated in the previous month. Medication adherence was evaluated using the 8-item Morisky Medication Adherence Scale (MMAS-8) having a score range of "0" to "8" with high scores indicating better adherence. Low adherence was defined as <6 points on MMAS-8.

Results: Over half of the group had active oral ulcers (n=219, 66.4%) within the month preceding the visit. The number of oral ulcers was significantly higher in female patients with low medication adherence (2.39±3.24) than in the rest of the female group (1.28±2.05; p=0.023). Although a similar trend was also observed in male patients (2.14±3.3 vs. 1.81±2.31), a significant relationship was not observed (p=0.89). The frequency of medication intake per day was lower in patients with high medication adherence than in the rest of the study group (p=0.04).

Conclusion: Low medication adherence is a hidden risk factor in the management of BD. Poor adherence was associated with oral ulcer activity in female BD patients.

Keywords: Medication adherence, oral ulcer, Behçet's disease

Introduction

Medication adherence is an important issue in the healthcare system (1) as symptom control, reductions in mortality and morbidity, and improvement in outcomes are the main treatment goals. A lack of medication adherence leads to an increase in unnecessary visits, hospitalizations (2), and medication costs (3, 4). Health policy makers aim to decrease these because of critical economic issues (1, 5-8). Medication adherence is mainly affected by the patients themselves, the healthcare system, the disease pattern, and treatment-related factors. Patient-related factors are defined as the demographic profile, beliefs, and socio-economic factors, including the patient's level of education and financial status. Beliefs can be categorized as concerns about the side effects of medications or an understanding of their beneficial effects. Healthcare system-related factors include the communication between patients and physicians and the utilization of health services, whereas disease-related factors are limited to symptom severity. Finally, the treatment-related factor is the complexity of treatment (9-11) with regard to the number of medications per day, the means of their administration, and the dosage frequency (7).

Behcet's disease (BD) is a multisystemic inflammatory chronic disorder characterized by remissions and relapses. Different treatment modalities using analgesics, nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and biological agents can be used for the treatment according to the type and severity of organ involvement. Oral ulcer is the most common clinical manifestation of BD. In contrast to immunosuppressive agents, conventional treatments using topical medications and colchicine could not eliminate oral ulcer activity (13-15). Therefore, this condition may be a barrier to medication adherence in cases of mucocutaneous involvement. Compliance to treatment has recently been evaluated by validation studies using the Morisky Medication Adherence Scale (MMAS), Compliance Questionnaire on Rheumatology (CQR-T), and Beliefs about Medicines Questionnaire in BD patients (16, 17). They have been found to be reliable tools for clinical practice. MMAS has also been found to be coherent with them (16, 17). The aim of this study was to evaluate the relationship between oral ulcer activity and medication adherence according to gender in BD patients.

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Material and Methods

This cross-sectional study included 330 consecutive BD patients (F/M: 167/163, mean age: 38.5±10.5 years) who were diagnosed according to the International Study Group criteria (18). Data were collected by clinical examinations and a questionnaire regarding medication adherence, the number of visits during the previous year, as well as the frequency of medications taken per day. The disease severity score was calculated according to organ involvement (19).

The inclusion criteria were using at least one medication within the last 3 months and being ≥18 years old at the time of the study. Inconsistent answers to items, mental health-related conditions, and comorbid factors related to medication usage (impairment in visual functions and poor physical condition) were the main exclusion criteria. The study was performed according to the principles of the Declaration of Helsinki and approved by the Ethical Committee of Marmara University Medical School. Informed consent was provided by all patients.

The primary outcome measure "adherence to treatment" was generated according to the self-reported adherence results from the preceding 4 weeks. Medication adherence was evaluated according to the 8-item MMAS (MMAS-8) translated in Turkish (20, 21). Permission for the use of the Turkish form was obtained from the corresponding author. Before starting the study, the translated questionnaire was controlled in accordance with cross-cultural adaptation guidelines (22). The scores of this scale range from "0" to "8," with high scores indicating better adherence. Low-adherence was defined as <6 points on MMAS-8 (20). Trained research assistants who were not involved in the treatment protocol administered the questionnaire to the patients during their regular scheduled visits. Content validity was evaluated by four experts (GM, NI, TE, and HD). Construct validity was assessed according to the frequency of medication intake per day and the number of visits during the previous year. Convergent validity was evaluated by forgetting medication intake with 5-point Likert-type scoring (1: none vs. 5: always). External reliability was assessed by test-retest analysis conducted on 5 % of patients over a 1-month period by a single researcher (GM), and interobserver reliability was evaluated by two researchers (GM and NI). The Cronbach alpha value for internal reliability was found to be 0.71.

Statistical analysis

Data were analyzed using the Statistical Packages for the Social Sciences SPSS 20.0 statistic program (IBM Corp.; Armonk, NY, USA). Unpaired t-test, chi-square test, and Pearson correlation test were used in the analysis. Mann-Whitney U test was used in in the non-normal distribution of the data.

Results

The clinical manifestations and demographic properties of patients are presented in Table 1. Patients were categorized into the "severe" group with major organ involvement (≥4 points) or the "mild" group with mucocutaneous symptoms (<4 points) according to their disease severity score (Table 1). Over half of the patients had active oral ulcers (n=219, 66.4%) within the month preceding the study. Over half of the patients (n=183, 55.5%) were treated with colchicine (1-2 mg/day), and the others (n=147, 44.5%) were given immunosuppressive medications (azathioprine and corticosteroids).

The score of MMAS-8 ranged from a low adherence level (<6 points; n=273, 82.7%) to medium/high levels (≥6 points; n=57, 17.3%). The ratio of patients with low medication adherence was higher in the mild disease course (57.5%) than in severe ones (42.5%; p=0.03; Table 2), especially with ocular involvement (33.7%; p=0.02). A similar relationship was not observed among the mild disease course and other severe organ involvements (p>0.05).

Table 1. Clinical manifestations and demographic properties of Behçet's disease patients

	n	%
Gender		
Female	167	50.6
Male	163	49.4
Organ Involvement		
Oral ulcer	330	100
Genital ulcer	288	87.3
Cutaneous	282	85.5
Musculo-skeletal	179	54.2
Ocular	105	31.8
Vascular	64	19.4
Neurological	18	5.5
Gastrointestinal	11	3.3
Disease Course		
Mild	181	54.8
Severe	149	45.2
Pathergy test (+)	199	60.3
	Mean	SD
Age (years)	38.5	10.5
Education status (years)	7.3	4.3
Disease duration (years)	11.3	7.5
Disease severity score	4.8	1.8

SD: standard deviation

Table 2. Medication adherence levels according to disease severity, gender, oral ulcer activity, and medication intake in Behçet's disease

		Low Medication Adherence n (%)	High Medication Adherence n (%)	p*
Disease Course	Mild	157 (57.5)	24 (42.1)	0.03
	Severe	116 (42.5)	33 (57.9)	
	Total	273 (100)	57 (100)	
Male	Oral Ulcer Active	84 (62.7)	20 (69)	0.52
	Oral Ulcer Inactive	50 (37.3)	9 (31)	
	Total	134 (100)	29 (100)	
Female	Oral Ulcer Active	101 (72.7)	14 (50)	0.018
	Oral Ulcer Inactive	38 (23.7)	14 (50)	
	Total	139 (100)	28 (100)	
		Mean±SD	Mean±SD	p
Medication Use	Frequency of Medication Intake/Day	2.6±0.8	2.4±0.6	0.04**
	Number of Medication Intake/Day	4.8±2.7	4.7±3.1	0.48***
Utilization of Healthcare	Number of Visits During the Previous Year	3.4±2.7	4.5±4.2	0.041***

SD: standard deviation *Chi-square test,**unpaired T test, and ***Mann-Whitney U test were used in the analysis

Moreover, the number of visits during the previous year was higher in patients with high medication adherence than in the others (p=0.041; Table 2). No significant difference was observed in the disease duration (low: 11.2±7.3 years vs. high: 11.8±8.4 years) and education year (low: 7.2±4.2 years vs. high: 7.3±4.5 years) according to medication adherence (p=0.59 and p=0.96, respectively).

In female BD patients, oral ulcer activity was significantly associated with low medication adherence (72.7%) compared with high medication adherence (50%; p=0.018), whereas a similar relationship was not observed in males (p=0.52; Table 2). In relation to this data, the number of oral ulcers was significantly higher in female patients with low medication adherence (2.39±3.24) than in the rest of the group (1.28±2.05; p=0.023). Although a similar trend was observed in male patients (2.14±3.3 vs. 1.81±2.31), a significant relationship was not observed (p=0.89).

In the study group, the frequency of medication intake per day was higher in the low medication adherence group than in the high medication adherence group (p=0.04; Table 2). The score of "forgetting medication intake" (2.38±1.04) moderately correlated with the MMAS-8 score (r=-0.6; p=0.000). In contrast, a similar relation was not observed in case of the number of daily medications (p=0.48; Table 2).

When 5% of the patients who were clinically stable were also evaluated for interobserver and intraobserver variations, no significant differences were observed in the intraobserver reliability (p>0.05). Interobserver reliability was evaluated by two researchers (GM and NI). No significant differences were found between the MMAS-8 scores of the researchers (p>0.05).

Discussion

Medication nonadherence is related to poor outcome and is a critical issue for health professionals, policymakers, as well as payers due to chronic conditions (23). It can be evaluated by measuring medication metabolites directly or indirectly using the patients' self-reported adherence levels (2). In the present study, low medication adherence was found in patients with a mild disease course and females with active oral ulcers. This may be explained by several factors. First, the treatment protocols of mucocutaneous manifestations are still unclear in cases of BD and total remission of mucocutaneous lesions usually cannot be achieved with the current approaches (24). Second, females with mucocutaneous involvement are less likely to be affected by potentially life-threatening complications. Therefore, the treatment of mucocutaneous disease is lesser aggressive that in case of major organ involvement. Lastly, patient expectations, which are usually "total cure," cannot be met in case of mucocutaneous involvement (12). Poor understanding of the illness and psychological distress may also be related to nonadherence to treatment regimens in females (25, 26).

In the study group, higher medication adherence was observed in patients with eye involvement than in those with mucocutaneous involvement. Because patients could easily understand the effect of treatment on their symptoms, flare-ups, daily life, and work ability, this result could be predicted.

As expected, the daily frequency of medication intake was related to low medication adherence. Our results were in accordance with the possible reasons for nonadherence such as forgetting medication and frequent dosing in previous studies (27). This can be improved through patient training, mainly highlighting the importance of adherence. Giving clear information and specified times for medications according to hourly intervals (e.g., every 6 h) or times per day (e.g., twice daily) and providing understandable instructions on labels helps patients use complex medication regimens safely and improves medication adherence (28).

Because nonadherence is not discussed regularly in clinical practice, it is often a hidden problem (29, 30). Clinicians are unable to recognize the condition as a reason for treatment failure, which then leads to unpredictable clinical activation or lack of disease control.

Another critical point is the complex medical protocols, including multiple medications and multiple daily doses per medication, which influence a patient's willingness to receive treatment. Nevertheless, future studies are necessary on BD in terms of the risk factors associated with nonadherence to medication regimens in different cultural groups.

This study had several limitations. First, it was designed to be a cross-sectional and observational study. The evaluation of adherence was performed using a self-reporting method. Metabolites of the medications involved were not examined. Second, the effect of cultural factors of medication adherence was not evaluated, necessitating future multicenter studies including patients from different countries. Third, medication adherence was evaluated on the physician's appointment. Although there were some limitations, the need of motivation and education was observed in patients with mucocutaneous involvement in the present study.

In conclusion, medication adherence was found to be low among the studied patient groups, and poor adherence was found to be associated with oral ulcer activity and gender in BD patients. MMAS-8 seems to be suitable for use in the routine clinical care of BD patients. Further studies addressing the consequences of constructed education programs targeting adherence improvement, which will provide critical information about the treatment issues, would be necessary.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University Medical School.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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